PRIOR AUTHORIZATION POLICY

**POLICY:** Inflammatory Conditions – Humira® (adalimumab for subcutaneous injection – AbbVie)

**DATE REVIEWED:** 10/18/2017

**OVERVIEW**
Humira is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody specific for human tumor necrosis factor (TNF)α. It neutralizes the biological activity of TNFα and inhibits binding of TNFα with its receptors. TNF, a naturally occurring cytokine, mediates inflammation and modulates cellular immune responses. Humira is indicated for the following uses:

1. to reduce the signs and symptoms, induce major clinical response, inhibit the progression of structural damage, and improve physical function in adult patients with moderately to severely active RA. Humira can be used alone or in combination with methotrexate (MTX) or other conventional synthetic disease-modifying antirheumatic drugs (DMARDs); AND
2. for reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 years of age and older. Humira can be used alone or in combination with MTX; AND
3. for reducing the signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with PsA. Humira can be used alone or in combination with conventional synthetic DMARDs; AND
4. for reducing signs and symptoms in patients with active AS; AND
5. for the treatment of adults with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy and when other systemic therapies are medically less appropriate; AND
6. for reducing signs and symptoms and inducing and maintaining clinical remission in adults with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy, including for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to Remicade® (infliximab intravenous [IV] infusion); AND
7. for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn’s disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine (6-MP), or MTX; AND
8. for inducing and sustaining clinical remission of moderately to severely active ulcerative colitis (UC) in adults who do not respond to corticosteroids or other immunosuppressive drugs such as azathioprine or 6-mercaptopurine. However, efficacy has not been established in patients with UC who have lost response or were intolerant to another TNF inhibitor (TNFi); AND
9. for the treatment of moderate to severe hidradenitis suppurativa (HS); AND
10. for uveitis, in adults with noninfectious intermediate, posterior, and panuveitis.

**Disease Overview**
TNF is a naturally occurring cytokine that mediates inflammation and modulates cellular immune responses. Increased levels of TNF have been implicated in the pathology of inflammatory conditions such as psoriasis, psoriatic arthritis, inflammatory bowel disease, and rheumatoid arthritis (RA). Increased levels of TNF are found in the synovial fluid of patients with RA, JIA, AS, and PsA; TNF has an important role in both the pathologic inflammation and the joint destruction that are characteristic of...
this disease. In psoriasis, increased levels of TNF are found in the blood and skin lesions. Adalimumab products binds to TNFα and inhibits binding of TNFα with its receptors.

**Guidelines**

TNFis feature prominently in guidelines for treatment of inflammatory conditions. Guidelines from the American College of Rheumatology (ACR) [2015] have TNFis (e.g., Cimzia® [certolizumab pegol SC injection], etanercept SC products [e.g., Enbrel®], adalimumab SC products [e.g., Humira®], infliximab IV products [e.g., Remicade®, Renflexis, Inflectra], Simponi® [golimumab SC injection], Simponi Aria® [golimumab IV infusion]) and non-TNF biologics (i.e., Actemra® [tocilizumab IV infusion, tocilizumab SC injection], Orencia® [abatacept IV infusion, abatacept SC injection], rituximab IV products [e.g., Rituxan®]), administered with or without MTX, equally positioned as a recommended therapy following a trial of a csDMARD (e.g., MTX, leflunomide, hydroxychloroquine, sulfasalazine). Other guidelines for inflammatory conditions (e.g., PsA [European Union Against Rheumatism; Group for Research and Assessment of Psoriasis and Psoriatic Arthritis {GRAPPA}] and spondylitis [AS and non-radiographic axial {nr-ax}SpA] {ACR and Spondylitis Association of America/Spondyloarthritides Research and Treatment Network}, inflammatory bowel disease [Crohn’s disease, UC] {American Gastroenterological Association} also note the significant place in therapy for TNFis.

**Safety**

Humira has Boxed Warnings concerning risks of serious infection and the risk of malignancy. Prior to initiating therapy, patients should be evaluated for active tuberculosis (TB) infection; periodically during therapy, patients should be assessed for latent TB infection. Patients should also be monitored for signs and symptoms of infection during and after treatment with Humira, and if a serious infection or sepsis develops, Humira should be discontinued. It is also noted that lymphoma and other malignancies have been reported in children and adolescents taking TNFis. There have also been reports of hepatosplenic T-cell lymphoma in adolescent and young adults treated with TNFis such as Humira.

**POLICY STATEMENT**

Prior authorization is recommended for prescription benefit coverage of Humira. Because of the specialized skills required for evaluation and diagnosis of patients treated with Humira as well as the monitoring required for adverse events (AEs) and long-term efficacy, initial approval requires Humira to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are for the duration noted below.

**Automation:** None.

**RECOMMENDED AUTHORIZATION CRITERIA**

Coverage of Humira is recommended in those who meet one the following criteria:

**FDA-Approved Indications**

1. **Rheumatoid Arthritis (RA):** Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) **Initial Therapy:** Approve for 3 months if the patient meets BOTH of the following criteria (i and ii):
i. The patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months (e.g., methotrexate [oral or injectable], leflunomide, hydroxychloroquine, and sulfasalazine).

NOTE: An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already had a 3-month trial at least one biologic (e.g., Cimzia [certolizumab pegol SC injection], an etanercept product [e.g., Enbrel], an infliximab product [e.g., Remicade, Renflexis, Inflectra] Simponi [golimumab SC injection], Simponi Aria [golimumab IV infusion], Actemra [tocilizumab IV infusion; tocilizumab SC injection], Kevzara [sarilumab SC injection], Kineret [anakinra SC injection], Orencia [abatacept IV infusion; abatacept SC injection], and a rituximab product [e.g., Rituxan]. These patients who have already tried a biologic for RA are not required to “step back” and try a conventional synthetic DMARD); AND

ii. Humira is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving Humira: Approve for 3 years if the patient has had a response (e.g., less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Humira.

Guidelines from the American College of Rheumatology (ACR) [2015] have TNF inhibitors and non-TNF biologics, administered with or without MTX, equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., MTX, leflunomide, hydroxychloroquine, sulfasalazine).19

2. Ankylosing Spondylitis (AS): Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) Initial Therapy: Approve for 3 months if prescribed by or in consultation with a rheumatologist.
   B) Patients Currently Receiving Humira: Approve for 3 years if the patient has had a response (e.g., decreased pain or stiffness, improved function or activities of daily living), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Humira.

3. Crohn’s Disease in a Patient ≥ 6 Years of Age: Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) Initial Therapy: Approve for 3 months if the patient meets the following criteria (i and ii):
      i. Patient meets ONE of the following conditions (a, b, c, or d):
         a) Patient has tried or is currently taking corticosteroids, or corticosteroids are contraindicated in this patient (Note: Examples of corticosteroids are prednisone, methylprednisolone); OR
         b) Patient has tried one other agent for Crohn’s disease (e.g., azathioprine, 6-mercaptopurine, methotrexate [MTX]).
         NOTE: A previous trial of a biologic (e.g., Cimzia [certolizumab pegol SC injection], Entyvio [vedolizumab IV infusion], infliximab product [e.g., Remicade, Inflectra, Renflexis], or Stelara [ustekinumab IV infusion, ustekinumab SC injection] also counts as a trial of one other agent for Crohn’s disease; OR
         c) The patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR
         d) The patient has had ileocolonic resection (to reduce the chance of Crohn’s disease recurrence); AND
      ii. Humira is prescribed by or in consultation with a gastroenterologist.
B) **Patients Currently Receiving Humira**: Approve for 3 years if the patient has had a response, as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Humira.

In addition to the approved indications, there are published data supporting the use of Humira for prevention of post-operative recurrence of Crohn’s disease. The American Gastroenterological Association (AGA) has guidelines for Crohn’s disease (2013). For induction therapy, TNFis are listed as a strong recommendation for patients with moderately severe Crohn’s disease (moderate-quality evidence). TNFi ± thiopurine is also mentioned as an appropriate regimen for maintenance of remission. Additionally, a global consensus which addresses perianal fistulizing Crohn’s disease (2014) notes that Humira is moderately effective for the induction and maintenance of fistula closure. It is stated that TNFis can be used as first-line medical treatment, optionally in combination with antibiotics and/or thiopurines. Of note, subgroup analysis from a Phase III study and other open-label studies have demonstrated efficacy of Humira in 23% to 33% of patients with fistulizing Crohn’s disease.

4. **Juvenile Idiopathic Arthritis (JIA) [or juvenile rheumatoid arthritis (JRA)] (regardless of type of onset)** [Note: This includes patients with juvenile spondyloarthropathy/active sacroiliac arthritis]: Approve for the duration noted if the patient meets ONE of the following (A or B):

A) **Initial Therapy**: Approve for 3 months if the patient meets the following criteria (i and ii):
   i. The patient meets ONE of the following conditions (a, b, c, or d):
      a) The patient has tried one other agent for this condition (e.g., methotrexate [MTX], sulfasalazine, leflunomide, or a nonsteroidal anti-inflammatory drug [NSAID] {e.g., ibuprofen, naproxen}).
      NOTE: A previous trial of a biologic (e.g., an etanercept product [e.g., Enbrel], an infliximab product [e.g., Remicade, Renflexis, Inflectra], Actemra [tocilizumab IV infusion], Kineret [anakinra SC injection], Orencia [abatacept IV infusion, abatacept SC injection]) also counts as a trial of one agent for JIA; OR
      b) The patient will be starting on Humira concurrently with methotrexate (MTX), sulfasalazine, or leflunomide; OR
      c) The patient has an absolute contraindication to methotrexate (MTX) [e.g., pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, blood dyscrasias], sulfasalazine, or leflunomide; OR
      d) The patient has aggressive disease, as determined by the prescribing physician; AND
   ii. Humira is prescribed by or in consultation with a rheumatologist.

B) **Patients Currently Receiving Humira**: Approve for 3 years if the patient has had a response (e.g., has improvement in limitation of motion; less joint pain or tenderness; decreased duration of morning stiffness or fatigue; improved function or activities of daily living; reduced dosage of corticosteroids), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Humira.

The 2011 ACR recommendations for the treatment of JIA propose initial DMARD treatment with MTX in most patients; however, sulfasalazine is recommended for patients with enthesitis-related arthritis and may also be used in certain patients with sacroiliac arthritis. Leflunomide may be an appropriate initial DMARD in certain patients with high disease activity and/or a poor prognosis. Kineret may be used in systemic arthritis and Actemra may be used in systemic and polyarticular juvenile arthritis arthritis. TNF antagonists may also be used as second- or third-line treatment for systemic JIA. The criteria for patients starting on Humira concurrently with a conventional
synthetic DMARD or for patients with an absolute contraindication MTX, sulfasalazine, or leflunomide are recommended based on the professional opinion of specialized physicians.

5. **Hidradenitis Suppurativa:** Approve for the duration noted if the patient meets ONE of the following (A or B):

   A) **Initial Therapy:** Approve for 3 months if the patient meets BOTH of the following (i and ii):
      i. The patient has tried ONE other therapy (e.g., intralesional or oral corticosteroids [such as triamcinolone, prednisone], systemic antibiotics [for example, clindamycin, dicloxacillin, erythromycin], isotretinoin); AND
      ii. Humira is prescribed by or in consultation with a dermatologist.

   B) **Patients Currently Receiving Humira:** Approve for 3 years if the patient has had a response, as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Humira.

In two Phase III pivotal studies in adults with moderate to severe hidradenitis suppurativa, between 40% and 50% of each treatment group had previously tried a systemic therapy. In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirements for previous therapy.

6. **Plaque Psoriasis:** Approve for the duration noted if the patient meets ONE of the following (A or B):

   A) **Initial Therapy:** Approve for 3 months if the patient meets the following criteria (i, ii, and iii):
      i. The patient is an adult greater than or equal to 18 years of age; AND
      ii. The patient meets ONE of the following conditions (a or b):
         a) The patient has tried at least one traditional systemic agent for psoriasis (e.g., methotrexate [MTX], cyclosporine, acitretin tablets, or psoralen plus ultraviolet A light [PUVA]) for at least 3 months, unless intolerant.
         NOTE: An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already has a 3-month trial or previous intolerance to at least one biologic (e.g., an etanercept product [e.g., Enbrel], an infliximab product [e.g., Remicade, Renflexis, Inflectra], Cosentyx® [secukinumab SC injection], Siliq [brodalumab SC injection], Stelara [ustekinumab SC injection], Taltz [ixekizumab SC injection], or Tremfya [guselkumab SC injection]). These patients who have already tried a biologic for psoriasis are not required to “step back” and try a traditional systemic agent for psoriasis); OR
         b) The patient has a contraindication to methotrexate (MTX), as determined by the prescribing physician; AND
      iii. Humira is prescribed by or in consultation with a dermatologist.

   B) **Patients Currently Receiving Humira:** Approve for 3 years if the patient has had a response, as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Humira.

Guidelines for treatment of plaque psoriasis recommend topical therapy for limited disease. However, for patients with chronic plaque psoriasis that does not respond to topical therapies or patients with more extensive disease, systemic therapy may be used. The traditional systemic agents for plaque psoriasis are MTX, Soriatane, and cyclosporine. An injectable biologic agent is an option for patients who are candidates for phototherapy or systemic therapy, especially those who are intolerant of or unresponsive to traditional systemic agents. In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirements for previous therapy.
7. **Psoriatic Arthritis (PsA):** Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) **Initial Therapy:** Approve for 3 months if Humira is prescribed by or in consultation with a rheumatologist or a dermatologist.
   B) **Patients Currently Receiving Humira:** Approve for 3 years if the patient has had a response (e.g., less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants [for example, C-reactive protein {CRP}]), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Humira.

In clinical trials, Humira was effective in patients with active PsA despite therapy with an NSAID. There are few well-controlled, prospective studies with adequate duration that have evaluated the efficacy of the oral DMARDs. Recommendations for the management of PsA have been developed by EULAR (2015) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) [2015]38-39 According to EULAR, treatment is recommended based on clinical presentation.38 In peripheral arthritis, a biologic (usually a TNFi) should be started if there is an inadequate response to at least one conventional synthetic DMARD. This recommendation is supported by the long-term experience and established safety/efficacy balance of TNFis vs. other biologics. In patients with enthesitis, dactylitis, or axial disease, the initial DMARD recommended is biologics; according to current practice a TNFi would be used. The guidelines note that comparison across trials is difficult because different outcomes were used. For enthesitis/dactylitis, the longest clinical experience is with TNFis. For axial disease, limited data exist for IL blockers. In patients who fail to respond to a biologic, switching to another biologic should be considered, including switching between TNFis. GRAPPA recommends TNFis for patients presenting with various manifestations of PsA (i.e., peripheral arthritis, axial disease, enthesitis, dactylitis, skin, and nail disease).39

8. **Ulcerative Colitis in an Adult:** Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) **Initial Therapy:** Approve for 3 months if the patient meets the following criteria (i and ii):
      i. The patient meets ONE of the following conditions (a or b):
         a) The patient has had a 2-month trial of one systemic agent (e.g., 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone or methylprednisolone) or was intolerant to one of these agents for ulcerative colitis. NOTE: A previous 2-month trial of a biologic [e.g., an adalimumab product [e.g., Humira], an infliximab product [e.g., Remicade, Renflexis, Inflectra], Simponi SC [golimumab SC injection], or Entyvio [vedolizumab IV infusion] also counts as a trial of one systemic agent for UC); OR
         b) The patient has pouchitis AND has tried therapy with an antibiotic (e.g., metronidazole, ciprofloxacin), probiotic, corticosteroid enema (e.g., hydrocortisone enema [Cortenema®, generics]), or Rowasa® (mesalamine) enema; AND
      ii. Humira is prescribed by or in consultation with a gastroenterologist.
   B) **Patients Currently Receiving Humira:** Approve for 3 years if the patient has had a response (e.g., decreased stool frequency or rectal bleeding), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Humira.

In addition to the approved indication, clinical guidelines for the management of pouchitis, published in 2009, and ulcerative colitis practice guidelines from the American College of Gastroenterology (ACG) [2010] indicate that first-line therapy for pouchitis is antibiotic therapy (e.g. metronidazole,
Other treatment options include maintenance probiotics, oral or topical budesonide, anti-inflammatory drugs (e.g., mesalamine), or immunosuppressive drugs (e.g., Remicade). A retrospective, open-label, case series demonstrated some efficacy of Humira in patients with pouchitis previously treated with Remicade. In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirements for pouchitis.

9. **Uveitis (including other posterior uveitides and panuveitis syndromes):** Approve for the duration noted if the patient meets ONE of the following (A or B):

   **A) Initial Therapy:** Approve for 3 months if the patient meets the following criteria (i and ii):
   
   i. The patient has tried ONE of the following therapies: periocular, intraocular, or systemic corticosteroids [for example, triamcinolone, betamethasone, methylprednisolone, prednisone] or immunosuppressives (e.g., methotrexate [MTX], mycophenolate mofetil, cyclosporine, azathioprine, cyclophosphamide) for this condition.
   
   NOTE: An exception to the requirement for a trial of one of these therapies can be made if the patient has already had a trial of an etanercept product [e.g., Enbrel] or an infliximab product [e.g., Remicade, Renflexis, Inflectra] for uveitis. These patients who have already tried a biologic for uveitis are not required to try a another agent; AND
   
   ii. Humira is prescribed by or in consultation with an ophthalmologist.

   **B) Patients Currently Receiving Humira:** Approve for 3 years if the patient has had a response, as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Humira.

In two Phase III pivotal studies evaluating Humira for uveitis, all patients were receiving oral prednisone. In one study (n = 217), patients had active disease despite use of oral prednisone, and in the other study (n = 226) uveitis was inactive while patients were on prednisone. All patients were tapered off prednisone by Week 15 (active uveitis study) or Week 19 (inactive uveitis study). In both studies, there was a significant reduction in the risk of treatment failure with Humira vs. placebo (78.5% and 55% rate of failure, respectively, with placebo and Humira in patients with active disease vs. 55% and 39% rate of failure, respectively, in patients with inactive disease while on prednisone). Recommendations for the use of TNFIs in ocular inflammatory disorders from the American Academy of Ophthalmology (AAO) [2014] note that Humira may be used in patients with uveitis due to various causes (e.g., spondyloarthropathy-associated or human leukocyte antigen [HLA]-B27-associated uveitis, JIA-associated uveitis, and other posterior uveitides and panuveitis syndromes). Humira should be considered second-line in vision-threatening JIA-associated uveitis when MTX has failed or is not tolerated (strong recommendation) and may be used as corticosteroid-sparing treatment for vision-threatening chronic uveitis from seronegative spondyloarthropathy (strong recommendation). Humira may also be considered in other patients who have vision-threatening or corticosteroid-dependent disease who have failed first-line therapies. The recommendations point out that a prospective study evaluated the efficacy of Humira in patients (n = 31) with a variety of uveitic conditions, including patients with idiopathic panuveitis and patients with birdshot chorioretinitis (BSCR), a bilateral posterior uveitis generally treated with systemic immunomodulation. Results showed a 68% response rate to Humira at Week 10 suggesting efficacy. Humira has been effective in children with noninfectious uveitis (either with rheumatic disease [JIA] or idiopathic) refractory to other therapies.

**Other Uses with Supportive Evidence**

10. **Behcet’s Disease:** Approve for 1 year if the patient meets the following criteria (A and B):

   **A)** The patient meets ONE of the following conditions (i or ii):

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i. The patient has tried at least ONE conventional therapy (e.g., systemic corticosteroids [for example, methylprednisolone], immunosuppressants [for example, azathioprine, methotrexate {MTX}, mycophenolate mofetil, cyclosporine, tacrolimus, Leukeran® {chlorambucil}, cyclophosphamide, interferon alfa]; OR
   NOTE: An exception to the requirement for a trial of one conventional therapy can be made if the patient has already had a trial of at least one biologic (e.g., an etanercept product [e.g., Enbrel] or an infliximab product [e.g., Remicade, Renflexis, Inflectra]). These patients who have already tried a biologic for Behcet’s disease are not required to “step back” and try a conventional therapy.

ii. The patient has ophthalmic manifestations of Behcet’s disease; AND

B) Humira is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist.

Recommendations for the use of TNFis in ocular inflammatory disorders from the American Academy of Ophthalmology (AAO) [2014] note that Humira may be used as first-line corticosteroid-sparing therapy in patients with ophthalmic manifestations of Behcet’s disease. In three cases, Humira was effective in controlling uveitis in adults with Behcet’s disease who were in remission after receiving Remicade. In another case series, six adults with Behcet’s disease (uveitis [two patients], central nervous system disease [two patients], colitis [one patient], and severe oral ulcers and arthritis [one patient]) in whom immunosuppressive therapy had failed, Humira was effective. These patients had received prior therapy with Remicade which had been discontinued after complete response or acceptable improvement. In a retrospective analysis (n = 11), Humira improved visual acuity and showed a corticosteroid and immunosuppressive sparing effect in ocular Behcet’s disease. Another review found 19 patients treated with Humira for Behcet’s disease, all of whom had refractory disease or experienced AEs to cyclosporine and Remicade. Overall, 17 out of 19 patients improved with Humira. In case reports, it has also been effective for neuro-Behcet’s and for treatment of leg ulcers in Behcet’s disease. EULAR recommendations for the management of Behcet disease include either Remicade or cyclosporine in combination with azathioprine and corticosteroids for refractory eye involvement. For gastrointestinal or parenchymal involvement, TNF antagonists have been resistant in long-term cases.

11. Pyoderma Gangrenosum: Approve for 1 year if the patient meets the following criteria (A and B):
   A) The patient meets ONE of the following conditions (i or ii):
      i. Patient has tried one systemic corticosteroid (e.g., prednisone); OR
      ii. Patient has tried one other immunosuppressant (e.g., mycophenolate mofetil, cyclosporine) for at least 2 months or was intolerant to one of these agents; AND
   B) The agent is prescribed by or in consultation with a dermatologist.

Multiple topical and systemic therapies have been used to treat pyoderma gangrenosum. Oral prednisone is the most common initial immunosuppressant medication. Topical therapies (e.g., corticosteroids, immunomodulators) may be applied to the lesion. Other systemic therapies used for treatment of pyoderma gangrenosum include cyclosporine, MTX, azathioprine, cyclophosphamide, mycophenolate mofetil, Remicade, Enbrel, and Humira. In case reports, Humira and other TNF antagonists have been effective in treating pyoderma gangrenosum. In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirements for previous therapy.

12. Sarcoidosis: Approve for 1 year if the patient meets the following criteria (A, B, and C):
   A) Patient has tried at least ONE corticosteroid for this condition (e.g., prednisone); AND
B) Patient has tried at least one immunosuppressive agent (e.g., methotrexate [MTX], azathioprine, cyclosporine, Leukeran, leflunomide, cyclophosphamide, mycophenolate mofetil), Remicade (infliximab IV infusion), chloroquine, or Thalomid® (thalidomide capsules); AND

C) The agent is prescribed by or in consultation with a pulmonologist, ophthalmologist, or dermatologist.

Well-controlled studies are not available for any therapies. Steroids are the standard therapy, although long-term use is limited by AEs.60 Immunosuppressants have shown modest efficacy with the best results available for MTX. High levels of TNF in bronchoalveolar lavage of patients with sarcoidosis have been reported with a decrease in TNF levels following treatment. Recommendations for best practice in the management of pulmonary and systemic sarcoidosis recommend glucocorticoids as first-line therapy.61 Patients who cannot be weaned to a prednisone-equivalent dose of < 10 mg/day are appropriate candidates for steroid-sparing treatment with cytotoxic agents (e.g., MTX, azathioprine, leflunomide). If these agents fail or cause toxicity, Humira, Remicade, cyclophosphamide, or mycophenolate mofetil are proposed. In a double-blind, placebo-controlled study, Humira was effective in improving clinical lesions and DLQI score in patients with cutaneous sarcoidosis (n = 16).62 In a prospective study in patients with refractory posterior uveitis (n = 26), intraocular inflammation improved and other indicators of disease activity, including pulmonary lung tests and laboratory tests, improved with Humira.63 Humira has also been effective in case reports of patients who were refractory to standard therapy.64-66 Recommendations for the use of TNFIs in ocular inflammatory disorders from the AAO (2014) note that Remicade or Humira may be considered as second-line immunomodulatory therapy for patients failing or intolerant of standard immunomodulatory agents (e.g., prednisone and MTX).42 In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirements for previous therapy.

13. Scleritis or Sterile Corneal Ulceration: Approve for 1 year if the patient meets the following criteria (A and B):

A) The patient has tried ONE other therapy for this condition (e.g., oral non-steroidal anti-inflammatory drugs [NSAIDs] such as indomethacin, naproxen, or ibuprofen; oral, topical [ophthalmic] or IV corticosteroids [such as prednisone, prednisolone, methylprednisolone]; methotrexate [MTX]; cyclosporine; or other immunosuppressants); AND

B) The agent is prescribed by or in consultation with an ophthalmologist.

Recommendations for the use of TNFIs in ocular inflammatory disorders from the AAO (2014) mention Humira as an agent that should be considered as a second-line immunomodulatory agent for severe ocular inflammatory conditions including chronic and severe scleritis.42

14. Spondyloarthritis (SpA), Subtypes Other than Ankylosing Spondylitis or Psoriatic Arthritis (e.g., undifferentiated arthritis, non-radiographic axial SpA, Reactive Arthritis [Reiter’s disease], arthritis associated with inflammatory bowel disease [IBD]) [NOTE: For AS or PsA, refer to the respective criteria under FDA-approved indications]: Approve for 1 year if BOTH of the following conditions are met (A and B):

A) The patient meets one of the following conditions (i or ii):

i. The patient has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet AND has tried at least ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) [e.g., methotrexate {MTX}, leflunomide, sulfasalazine] has been tried; OR

ii. The patient has axial spondyloarthritis; AND

B) The agent is prescribed by or in consultation with a rheumatologist.
SpA describes a group of inter-related rheumatic conditions that are distinguished according to their clinical presentation.\(^{67-68}\) (Note that AS and PsA are specific subtypes of SpA for which Humira is indicated and criteria are addressed in the FDA-approved indications of this policy.) SpA involves sites where ligaments and tendons attach to bones (entheses). Symptoms often include inflammation that leads to pain and stiffness. Axial SpA refers to inflammatory disease with a main symptom of back pain and includes AS (where x-ray damage is clearly present) and non-radiographic axial (nr-ax)SpA.\(^{69}\) In nr-axSpA, x-ray changes are not present, but there are symptoms. Upon magnetic resonance imaging (MRI), most patients with nr-axSpA have visible inflammation in the sacroiliac joints and/or the spine. Guidelines (2015) for AS and nr-axSpA are available from ACR/Spondylitis Association of America (SAA)/Spondyloarthritis Research Network (SPARTAN).\(^{20}\) TNFis are recommended for patients with nr-axSpA who have tried NSAIDs. Treatment recommendations for axial spondyloarthritis are available from the Assessment in SpondyloArthritis international Society (ASAS).\(^{70}\) These guidelines note that patients who present with axial SpA, including patients with nr-axSpA, should have a trial of at least two NSAIDS over a 4-week period at the maximum recommended or tolerated dose. Patients who have predominantly axial manifestations are not recommended for a conventional synthetic DMARD trial prior to beginning therapy with a TNFis. In patients with symptomatic peripheral arthritis, a therapeutic trial of a conventional synthetic DMARD is recommended (preferably sulfasalazine).

**15. Patient has been Established on Humira for ≥ 90 Days:** For conditions that do not have criteria for Patients Currently Receiving Humira but are indications or conditions addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications and Other Uses with Supportive Evidence), approve Humira for 1 year, if the patient is currently taking Humira for ≥ 90 days. (In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.)

**CONDITIONS NOT RECOMMENDED FOR APPROVAL**

Humira has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD):** Humira should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see APPENDIX for examples). Combination therapy is generally not recommended due to a potentially higher rate of AEs with combinations and lack of data supportive of additional efficacy.\(^{45}\) **Note:** This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Humira.

2. **Polymyalgia Rheumatica (PMR):** EULAR/ACR guidelines for the management of PMR (2015) strongly recommend against the use of TNFis for treatment of PMR.\(^{72}\) This recommendation is based on lack of evidence for benefit as well as considerable potential for potential harm.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.
REFERENCES
Inflammatory Conditions – Humira PA Policy

Page 12


Inflammatory Conditions – Humira PA Policy
Page 13


OTHER REFERENCES UTILIZED

### HISTORY

<table>
<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes*</th>
<th>TAC Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual revision</td>
<td>Update RA criteria to remove “in an adult” as a qualifier for diagnosis. Add criteria to approve fistulizing Crohn’s disease, if other conditions for coverage are met. Move hidradenitis suppurativa to an FDA-approved indication (previously approved as off-label indication). Add criteria for SpA and delete criteria for Undifferentiated Spondyloarthritids (now covered under SpA). Add PMR as a Condition Not Recommended for Approval.</td>
<td>09/30/2015</td>
</tr>
<tr>
<td>Selected revision</td>
<td>Update previous therapy required in the RA criteria. Criteria now require a trial of a conventional synthetic DMARD. There is an exception for patients who have already tried a biologic; these patients are not required to “step back” and try a conventional synthetic DMARD. Remove other exceptions for patients who are not required to try a conventional synthetic DMARD prior to this biologic.</td>
<td>01/06/2016</td>
</tr>
<tr>
<td>Selected revision</td>
<td>For psoriasis, the criterion that allows an exception for patients with a contraindication to one traditional oral therapy is being adjusted to specify a contraindication to MTX. In addition, the psoriasis criteria concerning previous therapy are being reworded for clarification.</td>
<td>04/06/2016</td>
</tr>
<tr>
<td>DEU revision</td>
<td>07/15/2016: Move Uveitis from Other Uses with Supportive Evidence to FDA-Approved indications. No changes to the Uveitis criteria.</td>
<td>07/15/2016</td>
</tr>
<tr>
<td>Annual revision</td>
<td>For Uveitis and Hidradenitis Suppurativa, change initial approval to 3 months and add criteria that approves for 3 years, if the patient is currently taking and has responded to therapy, as determined by the prescribing physician. Remove Osteoarthritis from the Conditions Not Recommended For Coverage (not needed). Add Stelara as an example of a medication a patient may have tried for Crohn’s disease. Add Simponi SC as an example of a medication a patient may have tried for ulcerative colitis.</td>
<td>10/19/2016</td>
</tr>
<tr>
<td>Annual revision</td>
<td>For RA, Kevzara was added as an example of an agent that may have been tried prior to Humira. Throughout the policy, criteria that mentioned Enbrel, Remicade, and Rituxan were reworded as etanercept, infliximab, and rituximab products, respectively, with the innovator names listed as examples of these products; Renflexis and Inflectra were also added to criteria as examples of an infliximab product. Criteria were clarified for Crohn’s disease, UC, Behcet’s disease, JIA, and uveitis. For these conditions, the criterion that directs patients to previous therapy prior to approval of adalimumab was reworded to clarify its intent such that patients are now directed to conventional agents with a note that prior use of a biologic would count towards this requirement. Previously, criteria were worded more generally and both conventional and biologic therapies were listed together. For plaque psoriasis, Siliq and Tremfya were added as examples of an agent that may have been tried prior to Humira. For initial therapy of plaque psoriasis, add criteria to require the patient is 18 years of age or greater.</td>
<td>10/18/2017</td>
</tr>
</tbody>
</table>

* For a further summary of criteria changes, refer to respective TAC minutes available at: [http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx](http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx); TAC – Therapeutic Assessment Committee; UC – Ulcerative colitis; CD – Crohn’s disease; DMARD – Disease-modifying antirheumatic drug; DEU – Drug Evaluation Unit; PJIA – Polyarticular juvenile idiopathic arthritis; NA – Not applicable; RA – Rheumatoid arthritis; SpA – Spondyloarthritis; PMR – Polymyalgia rheumatic; MTX – Methotrexate.
## APPENDIX

<table>
<thead>
<tr>
<th>Brand (generic name)</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimzia® (certolizumab pegol for SC injection)</td>
<td>Inhibition of TNF</td>
</tr>
<tr>
<td>Enbrel® (etanercept for SC injection)</td>
<td>Inhibition of TNF</td>
</tr>
<tr>
<td>Erelzi® (etanercept-szsz for SC injection)</td>
<td>Inhibition of TNF</td>
</tr>
<tr>
<td>Humira® (adalimumab for SC injection)</td>
<td>Inhibition of TNF</td>
</tr>
<tr>
<td>Amjevita® (adalimumab-atto for SC injection)</td>
<td>Inhibition of TNF</td>
</tr>
<tr>
<td>Simponi® (golimumab for SC injection)</td>
<td>Inhibition of TNF</td>
</tr>
<tr>
<td>Simponi® Aria™ (golimumab for IV infusion)</td>
<td>Inhibition of TNF</td>
</tr>
<tr>
<td>Remicade® (infliximab for IV infusion)</td>
<td>Inhibition of TNF</td>
</tr>
<tr>
<td>Inflectra™ (infliximab-dyyb for IV infusion)</td>
<td>Inhibition of TNF</td>
</tr>
<tr>
<td>Remiflexis® (infliximab-abda for IV infusion)</td>
<td>Inhibition of TNF</td>
</tr>
<tr>
<td>Actemra® (tocilizumab for IV infusion)</td>
<td>Inhibition of IL-6</td>
</tr>
<tr>
<td>Actemra® (tocilizumab for SC injection)</td>
<td>Inhibition of IL-6</td>
</tr>
<tr>
<td>Kevzara® (sarilumab for SC injection)</td>
<td>Inhibition of IL-6</td>
</tr>
<tr>
<td>Orencia® (abatacept for IV infusion)</td>
<td>T-cell costimulation modulator</td>
</tr>
<tr>
<td>Orencia® (abatacept for SC injection)</td>
<td>T-cell costimulation modulator</td>
</tr>
<tr>
<td>Rituxan® (rituximab for IV infusion)</td>
<td>CD20-directed cytolytic antibody</td>
</tr>
<tr>
<td>Kineret® (anakinra for subcutaneous SC injection)</td>
<td>Inhibition of IL-1</td>
</tr>
<tr>
<td>Stelara® (ustekinumab for SC injection)</td>
<td>Inhibition of IL-12/23</td>
</tr>
<tr>
<td>Stelara® (ustekinumab for IV infusion)</td>
<td>Inhibition of IL-12/23</td>
</tr>
<tr>
<td>Siliq™ (brodalumab SC injection)</td>
<td>Inhibition of IL-17</td>
</tr>
<tr>
<td>Cosentyx™ (secukinumab for SC injection)</td>
<td>Inhibition of IL-17A</td>
</tr>
<tr>
<td>Taltz® (ixekizumab for SC injection)</td>
<td>Inhibition of IL-17A</td>
</tr>
<tr>
<td>Tremfya® (guselkumab for SC injection)</td>
<td>Inhibition of IL-23</td>
</tr>
<tr>
<td>Otezla® (apremilast tablets)</td>
<td>Inhibition of PDE4</td>
</tr>
<tr>
<td>Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)</td>
<td>Inhibition of the JAK pathways</td>
</tr>
</tbody>
</table>

SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase.